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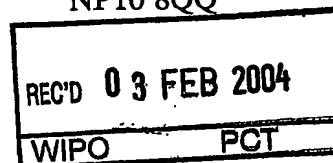


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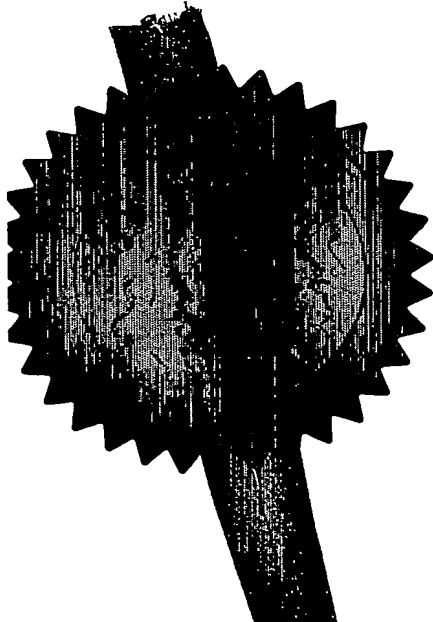


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Dated 22 January 2004



23DEC02 E772572-1 003022  
P01/7700 0.00-0229683.8

THE PATENT OFFICE

20 DEC 2002

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The Patent Office

Cardiff Road  
Newport  
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1. Your reference PZ 02109

20 DEC 2002

2. Patent application number  
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0229683.8

3. Full name, address and postcode of the or of each applicant (underline all surnames)

IMAGING RESEARCH SOLUTIONS LTD  
Cyclotron Building  
Hammersmith Campus  
DuCane Road  
London  
W12 0NN

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

8177883001

4. Title of the invention

PREPARATION OF RADIOPHARMACEUTICALS

5. Name of your agent (if you have one)

HAMMETT, Audrey, Grace, Campbell; ROLLINS, Anthony, John and HAMMER, Catriona, MacLeod

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

Amersham plc  
Amersham Place  
Little Chalfont  
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6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application number  
(if you know it)

Date of filing  
(day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing  
(day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

Yes

- a) any applicant named in part 3 is not an inventor, or
  - b) there is an inventor who is not named as an applicant, or
  - c) any named applicant is a corporate body.
- See note (d))

## Patents Form 1/77

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### Continuation sheets of this form

Description	12
Claim(s)	5
Abstract	0
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### Priority documents

#### Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

1

Request for substantive examination (*Patents Form 10/77*)

Any other documents  
(please specify)

11. I/We request the grant of a patent on the basis of this application.

  
HAMMETT, Audrey, Grace, Campbell

Signature

Date

18 December 2002

12. Name and daytime telephone number of person to contact in the United Kingdom HAMMETT, Audrey  
01494 542747

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PREPARATION OF RADIOPHARMACEUTICALS **DUPLICATE**

5 The present invention relates to novel processes for the production of radiolabelled tracers, in particular for the production of  $^{18}\text{F}$ -labelled compounds such as  $5[^{18}\text{F}]$ fluorouracil and  $5[^{18}\text{F}]$ fluorocytosine which may be suitable for use as Positron Emission Tomography (PET) radiotracers. The invention also comprises radiopharmaceutical kits using these novel processes.

10 The favoured radioisotope for PET,  $^{18}\text{F}$ , has a relatively short half-life of 110 minutes.  $^{18}\text{F}$ -labelled tracers for PET therefore have to be synthesised and purified as rapidly as possible, and ideally within one hour of clinical use. Standard synthetic methods for introducing fluorine-18 are relatively slow and require post-reaction purification (for example, by HPLC) which means that it is difficult to obtain the  $^{18}\text{F}$ -labelled tracer for clinical use in good radiochemical yield.  
15 There is also a need for automation to protect the operator from radiation exposure. Many radiofluorinations are complicated procedures and it is necessary to simplify them to facilitate automation.

20 The present invention provides solution- and solid-phase processes for producing  $^{18}\text{F}$ -labelled tracers quickly and with high specific activity yet avoiding time-consuming purification steps, such that the resultant  $^{18}\text{F}$ -labelled tracer is suitable for use in PET. The solid-phase methods particularly also lend themselves to automation with advantages of ease of production and greater throughput. The invention also comprises radiopharmaceutical kits which use such processes and  
25 thus provide the radiopharmacist or clinician with a convenient means of preparing an  $^{18}\text{F}$ -labelled tracer.

Solid-phase nucleophilic fluorination methods are described in co-pending International Patent Application PCT/GB02/02505.

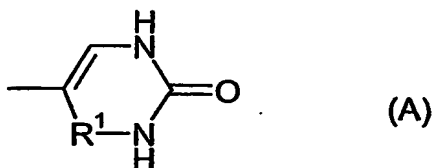
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According to a first aspect, the invention provides a process for the production of an  $^{18}\text{F}$ -labelled tracer which comprises treatment of a solid support-bound

precursor of formula (I):

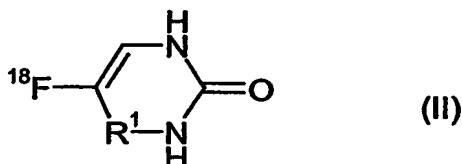


wherein the TRACER is of formula (A):



wherein  $\text{Y}^-$  is an anion, preferably trifluoromethylsulphonate (triflate) anion; and  $\text{R}^1$  is either (i) a group  $\text{CH-NP}^{1A}\text{P}^{2A}$  in which  $\text{P}^{1A}$  and  $\text{P}^{2A}$  are each independently hydrogen or a protecting group, or (ii) a carbonyl group;

with  $^{18}\text{F}^-$  to produce the labelled tracer of formula (II)



wherein  $\text{R}^1$  is as defined for the compound of formula (I); optionally followed by:

- (i) removal of excess  $^{18}\text{F}^-$ , for example by ion-exchange chromatography; and/or
- (ii) removal of any protecting groups; and/or
- (iii) removal of organic solvent; and/or
- (iv) formulation of the resultant compound of formula (II) as an aqueous solution.

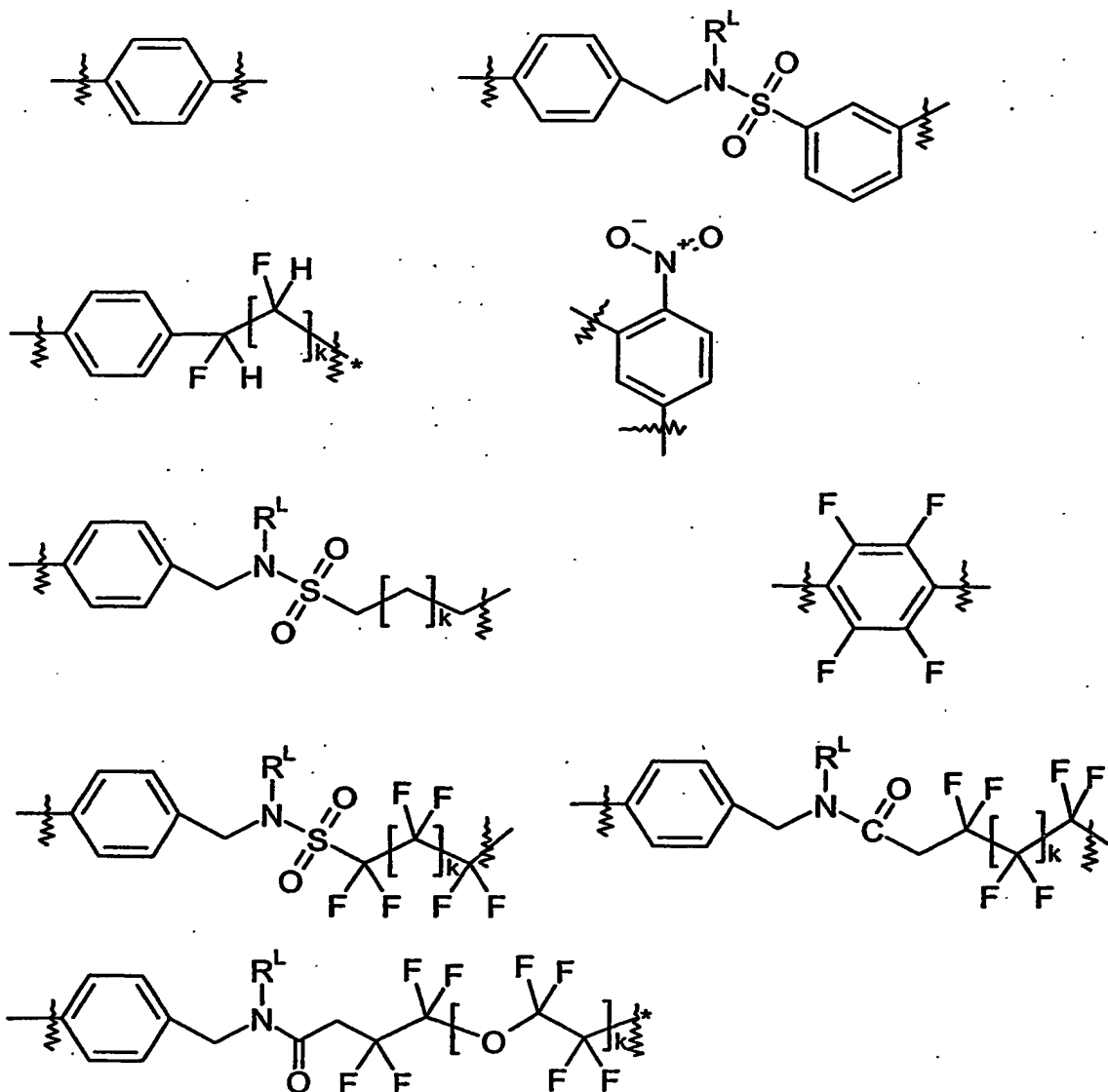
The compound of formula (I) may be conveniently prepared from a functionalised commercially available resin such as a Merrifield Resin or Wang Resin. Suitably, a hydroxyiodoaryl (such as an iodophenol) containing LINKER group is treated with an inorganic base, such as cesium carbonate and then added to the resin, pre-swollen with an inert solvent, such as N,N-dimethylformamide and allowed to

react at elevated temperature, for example 30 to 80°C. Excess reagents may be removed by washing the resin with further inert solvent. The resultant iodophenol functionalised resin may then be treated with a source of acetate anions (such as acetic acid, acetic anhydride, or acetyl chloride) in the presence of an oxidising agent, such as hydrogen peroxide to provide the corresponding diacetoxyl-iodophenyl functionalised resin. The diacetoxyl-iodophenyl functionalised resin may then be stirred in an inert solvent, such as dichloromethane, in the presence of acid such as hydrochloric acid, trifluoromethane sulphonic acid, or acetic acid at a low temperature, suitably -40°C to 10°C before addition of the tracer, suitably functionalised as a boronic acid or triorgano tin (suitably trialkyl tin) derivative which may be coupled to the resin at a non-extreme temperature. As in previous steps, the desired compound of formula (I) may be separated by filtration and washing with an inert solvent.

As the  $^{18}\text{F}$ -labelled tracer of formula (II) is removed from the solid-phase into solution, all unreacted precursor remains bound to the resin and can be separated by simple filtration, thus obviating the need for complicated purification, for example by HPLC. The  $^{18}\text{F}$ -labelled tracer of formula (II) may be cleaned up by removal of excess  $\text{F}^-$ , for example by ion-exchange chromatography and/or by removal of any organic solvent. The resultant  $^{18}\text{F}$ -labelled tracer of formula (II) may then be further made-up into an aqueous formulation for clinical use.

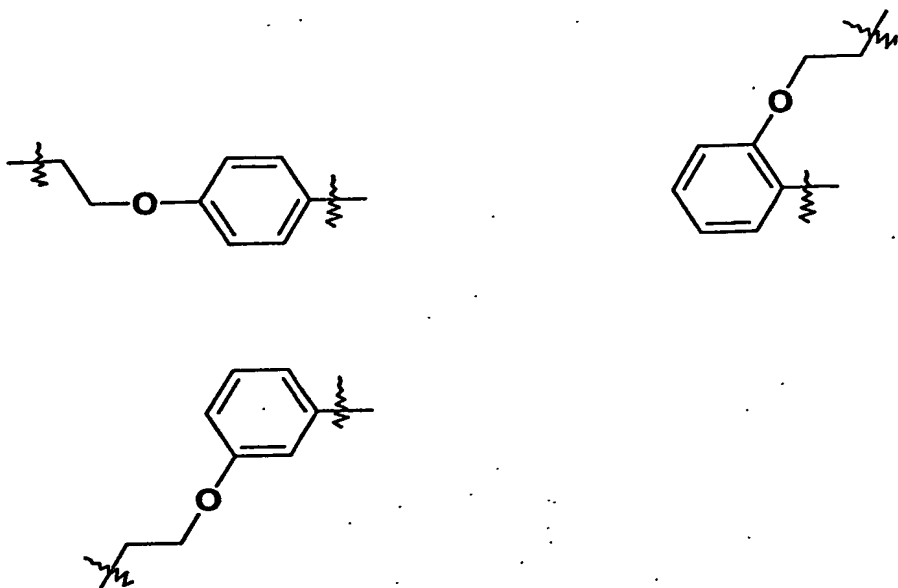
In the compounds of formulae (I) and in the following more specific aspects of the invention, the "SOLID SUPPORT" may be any suitable solid-phase support which is insoluble in any solvents to be used in the process but to which the LINKER and/or TRACER can be covalently bound. Examples of suitable SOLID SUPPORT include polymers such as polystyrene (which may be block grafted, for example with polyethylene glycol), polyacrylamide, or polypropylene or glass or silicon coated with such a polymer. The solid support may be in the form of small discrete particles such as beads or pins, or as a coating on the inner surface of a cartridge or on a microfabricated vessel.

- In the compounds of formulae (I) and in the following more specific aspects of the invention, the "LINKER" may be any suitable organic group which serves to space the reactive site sufficiently from the solid support structure so as to maximise reactivity. Suitably, the LINKER comprises zero to four aryl groups (suitably phenyl) and/or a C<sub>1-6</sub> alkyl or C<sub>1-6</sub> haloalkyl (suitably C<sub>1-6</sub> fluoroalkyl), and optionally one to four additional functional groups such as amide or sulphonamide groups. Examples of such linkers are well known to those skilled in the art of solid-phase chemistry, but include:

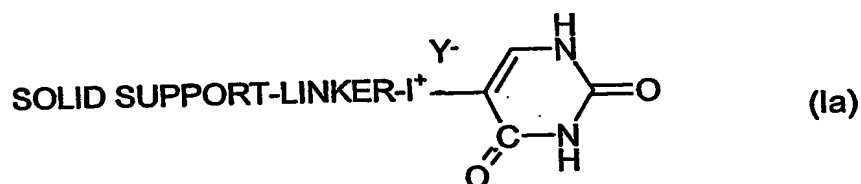


wherein at each occurrence, k is an integer of 0 to 3 and R<sup>L</sup> is hydrogen or C<sub>1-6</sub> alkyl.

In the compound of formula (I) and in the following more specific aspects of the invention, the LINKER is as defined above but suitably comprises an aryl group (suitably phenyl) adjacent to the  $I^+$ . Preferred examples include

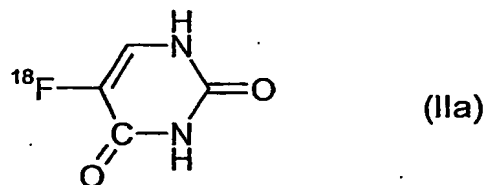


The present invention provides in a further aspect, a process for the production of  $5[^{18}\text{F}]$ fluorouracil which comprises treatment of a solid support-bound precursor of formula (Ia):



1.5 wherein  $Y^-$  is an anion, preferably trifluoromethylsulphonate (triflate) anion; with  $^{18}\text{F}^-$  to produce the labelled tracer of formula (IIa)

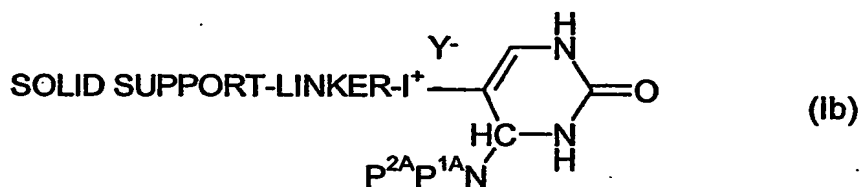




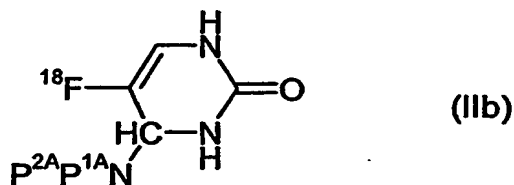
optionally followed by :

- (i) removal of excess  $^{18}\text{F}^-$  , for example by ion-exchange chromatography; and/or
- 5 (ii) removal of organic solvent; and/or
- (iii) formulation of the resultant compound of formula (IIa) as an aqueous solution.

The present invention provides in a further aspect, a process for the production of 5[ $^{18}\text{F}$ ]fluorocytosine which comprises treatment of a solid support-bound precursor of formula (Ib):



wherein  $\text{Y}^-$  is an anion, preferably trifluoromethylsulphonate (triflate) anion,  $\text{P}^{1\text{A}}$  and  $\text{P}^{2\text{A}}$  are independently hydrogen or a protecting group; with  $^{18}\text{F}$  to produce the labelled tracer of formula (IIb)



- 20 wherein  $\text{P}^{1\text{A}}$  and  $\text{P}^{2\text{A}}$  are as defined for the compound of formula (Ib), optionally followed by:
  - (i) removal of excess  $^{18}\text{F}^-$  , for example by ion-exchange chromatography; and/or
  - (ii) removal of organic solvent; and/or

- (iii) removal of any protecting groups; and/or
- (iv) formulation of the resultant compound of formula (IIb) as an aqueous solution.

As would be apparent to the person skilled in the art, it may be necessary to protect functional groups in the TRACER to avoid unwanted reactions during the radiolabelling process. Such protection may be achieved using standard methods of protecting group chemistry. After the radiolabelling is complete, any protecting groups may be removed by simple procedures which are also standard in the art.

Suitable protection and deprotection methodologies may be found, for example, in *Protecting Groups in Organic Synthesis*, Theodora W. Greene and Peter G. M. Wuts, published by John Wiley & Sons Inc. For example, the amine functionality in the compound of formula (I) may be protected as esters, suitably C<sub>1-6</sub> alkyl esters, preferably as acyl esters such as t-butoxycarbonyl, or ethers, preferably as C<sub>1-6</sub> alkyl ethers, or amides. These protecting groups may be conveniently removed by hydrolysis, for example in the presence of acid or base. Such deprotection may be effected using a solid supported acid or base catalysts that render the need for post deprotection neutralisation unnecessary.

Treatment of the compound of formula (I), (Ia), or (Ib) with <sup>18</sup>F<sup>-</sup> may be effected by treatment with any suitable source of <sup>18</sup>F<sup>-</sup>, such as Na<sup>18</sup>F, K<sup>18</sup>F, Cs<sup>18</sup>F, tetraalkylammonium <sup>18</sup>F fluoride, or tetraalkylphosphonium <sup>18</sup>F fluoride. To increase the reactivity of the fluoride, a phase transfer catalyst such as 4,7,13,16,21,24 hexaoxa-1,10-diazabicyclo[8,8,8] hexacosane may be added and the reaction performed in a non protic solvent. These conditions give reactive fluoride ions. The treatment with <sup>18</sup>F<sup>-</sup> is suitably effected in the presence of a suitable organic solvent such as acetonitrile, dimethylformamide, dimethylsulphoxide, tetrahydrofuran, dioxan, 1,2 dimethoxyethane, sulpholane, N-methylpyrrolidine, at a non-extreme temperature, for example, 15°C to 180°C, preferably at elevated temperature. On completion of the reaction, the <sup>18</sup>F-labelled tracer of formula (II) dissolved in the solvent is conveniently separated from the solid-phase by filtration. The same fluorination techniques may be used in the other aspects of the invention.

Any excess  $^{18}\text{F}^-$  may be removed from the solution of  $^{18}\text{F}$ -tracer by any suitable means, for example by ion-exchange chromatography or solid phase absorbents.

Suitable ion-exchange resins include BIO-RAD AG 1-X8 or Waters QMA and  
5 suitable solid phase absorbents include alumina. The excess  $^{18}\text{F}^-$  may be removed using such solid phases at room temperature in aprotic solvents.

Any organic solvent may be removed by any standard method such as by evaporation at elevated temperature *in vacuo* or by passing a stream of inert gas  
10 such as nitrogen or argon over the solution.

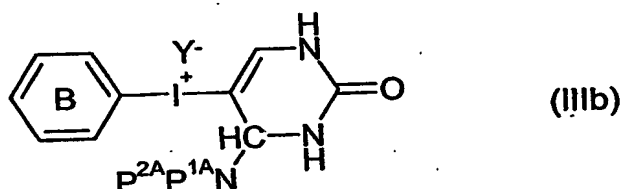
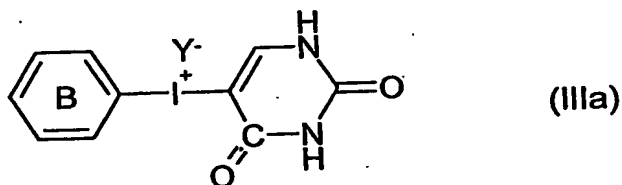
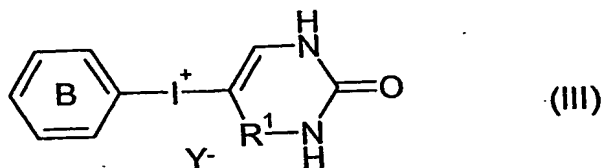
Before use of the  $^{18}\text{F}$ -labelled tracer, it may be appropriate to formulate it, for example as an aqueous solution by dissolving the  $^{18}\text{F}$ -labelled tracer in sterile isotonic saline which may contain up to 10% of a suitable organic solvent such as  
15 ethanol, or a suitable buffered solution such as phosphate buffer. Other additives may be added such as ascorbic acid to reduce radiolysis.

The compounds of formula (I) are novel and thus form a further aspect of the present invention. Thus, for example, compounds of formula (Ia) and formula (Ib)  
20 also form separate aspects of the present invention.

As described above, the advantages of such solid-phase processes for preparation of  $^{18}\text{F}$ -labelled tracers include the relative speed of the process, simplified purification methods and ease of automation- all of which mean that the  
25 processes are suitable for preparation of  $^{18}\text{F}$ -labelled tracers for use in PET. Accordingly, the present invention provides a process according to the invention for the production of a  $^{18}\text{F}$ -labelled tracer of formula (II), (IIa), or (IIb) for use in PET.

30 In an alternative aspect of the invention, the compounds of formula (II), (IIa), and (IIb) can also be prepared by analogous solution phase methods. Accordingly, there is provided a process for the production of an  $^{18}\text{F}$ -labelled tracer which

comprises treatment of a compound of formula (III), (IIIa), or (IIIb):



- 5 wherein R<sup>1</sup>, P<sup>2A</sup>, P<sup>1A</sup>, and Y<sup>-</sup> are as defined in formula (I), and phenyl ring B is optionally substituted with one to five substituents independently selected from halo, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, hydroxy, C<sub>1-6</sub> alkoxy, amino, C<sub>1-6</sub> hydroxyalkyl, and nitro;
- 10 with <sup>18</sup>F<sup>-</sup> to produce the labelled tracer of formula (II), (IIa), or (IIb) respectively as defined above, optionally followed by:

- (i) removal of excess <sup>18</sup>F<sup>-</sup>, for example by ion-exchange chromatography; and/or
- (ii) removal of any protecting groups; and/or
- 15 (iii) removal of organic solvent; and/or
- (iv) formulation of the resultant compound of formula (II), (IIa), or (IIb) as an aqueous solution.

20 Conveniently, the solid support bound precursor of formula (I) or a compound of formula (III), (IIIa), or (IIIb) could be provided as part of a kit to a radiopharmacy.

The kit may contain a cartridge which can be plugged into a suitably adapted automated synthesiser. The cartridge may contain, apart from the precursor compound, a column to remove unwanted fluoride ion, and an appropriate vessel connected so as to allow the reaction mixture to be evaporated and allow the

product to be formulated as required. The reagents and solvents and other consumables required for the synthesis may also be included together with a compact disc carrying the software which allows the synthesiser to be operated in a way so as to meet the customers requirements for radioactive concentration, volumes, time of delivery etc.

Conveniently, all components of the kit are disposable to minimise the possibilities of contamination between runs and may be sterile and quality assured.

The invention further provides a radiopharmaceutical kit for the preparation of an  $^{18}\text{F}$ -labelled tracer for use in PET, which comprises:

- (i) a vessel containing a compound of formula (I), (Ia), (Ib), (III), (IIIa), or (IIIb); and
- (ii) means for eluting the vessel with a source of  $^{18}\text{F}^-$ ;
- (iii) an ion-exchange cartridge for removal of excess  $^{18}\text{F}^-$ ; and optionally
- (iv) a cartridge for solid-phase deprotection of the resultant product of formula (II), (IIa), or (IIb).

The invention further provides a cartridge for a radiopharmaceutical kit for the preparation of an  $^{18}\text{F}$ -labelled tracer for use in PET which comprises:

- (i) a vessel containing a compound of formula (I), (Ia), (Ib), (III), (IIIa), or (IIIb); and
- (ii) means for eluting the vessel with a source of  $^{18}\text{F}^-$ .

In a further aspect of the invention, there is provided a method for obtaining a diagnostic PET image which comprises the step of using a radiopharmaceutical kit or a cartridge for a radiopharmaceutical kit as described above.

The invention will now be illustrated by way of the following Examples.

Throughout the Examples, abbreviations used are as follows:

- DMF: N,N-dimethylformamide
- w/v : weight/volume
- h : hour(s)

tlc : thin layer chromatography

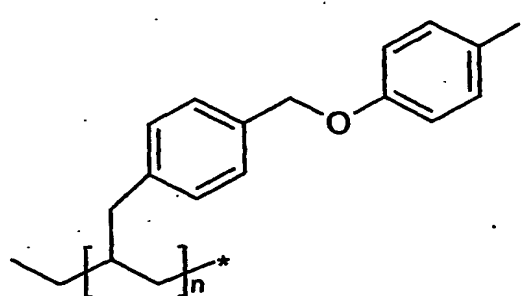
THF : tetrahydrofuran

eq. : equivalents

## 5 Examples

### Example 1 – Synthesis of 5[<sup>18</sup>F]-fluorouracil

#### Example 1 (i) Synthesis of PS iodo-phenyl benzyl ether

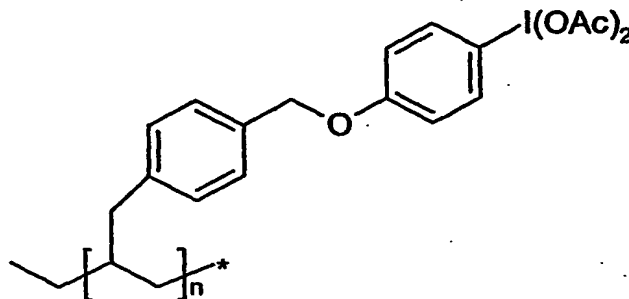


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To a suspension of Wang Resin pre-swollen in DMF (2ml) a solution of cesium carbonate and iodophenol in DMF were added. The mixture was stirred for 3h at 60°C and then left at room temperature overnight. After filtration the resin was washed consecutively with methanol, dichloromethane, DMF and THF before thorough drying under high vacuum.

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#### Example 1 (ii) Synthesis of PS diacetoxy-iodo-phenyl benzyl ether

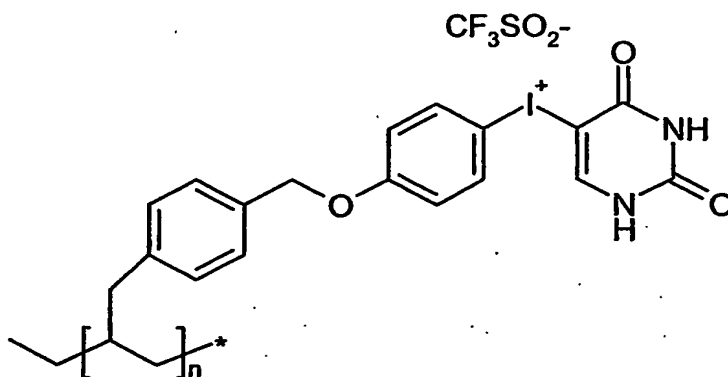


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A suspension of the resin above was treated with acetic anhydride and hydrogen peroxide (see method of S.Ficht, Tetrahedron, 57 (2001) 4863) in a 4:1 ratio at

40°C overnight. The resin was then filtered and washed thoroughly with methanol and then dried under high vacuum until dry.

Example 1 (iii) – Synthesis of solid-support bound precursor for 5[<sup>18</sup>F]-fluorouracil



5

To a suspension of the resin from Example 1(ii) above in dichloromethane, trifluoromethane sulfonic acid is added dropwise at a temperature of –30°C for 15 minutes. The mixture is then warmed to 0°C for a further 15 minutes before being stirred at room temperature overnight. The suspension is then cooled to –30°C and 5-dihydroxyboranyl-1H-pyrimidine-2,4-dione (Schinazi *et al*, Tetrahedron Lett.; 1978, 4981) is added, and the suspension is stirred for 1h before warming to room temperature and further stirring overnight. The mixture is then filtered and washed thoroughly with dichloromethane and diethyl ether before drying under vacuum.

15

Example 1(iv) – Radiofluorination to prepare 5[<sup>18</sup>F]- fluorouracil

To a portion of the resin from Example 1(iii) held in a cartridge is added a solution in dry acetonitrile of kryptofix, potassium carbonate and [<sup>18</sup>F]-fluoride. The suspension is heated to 85°C for 10 minutes and then the solution is filtered off. The resin is washed with acetonitrile (1ml) and all the contents collected together before evaporation of the solvent prior to formulation.

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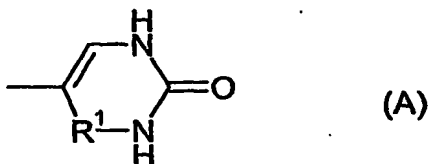
Claims

1. A process for the production of an  $^{18}\text{F}$ -labelled tracer which comprises  
 5 treatment of a solid support-bound precursor of formula (I):



$$\text{Y}^-$$

wherein the TRACER is of formula (A):

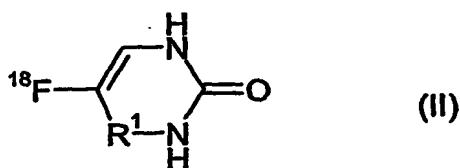


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wherein  $\text{Y}^-$  is an anion, preferably trifluoromethylsulphonate (triflate) anion; and  
 $\text{R}^1$  is either (i) a group  $\text{CH-NP}^{1\text{A}}\text{P}^{2\text{A}}$  in which  $\text{P}^{1\text{A}}$  and  $\text{P}^{2\text{A}}$  are each independently  
 hydrogen or a protecting group, or (ii) a carbonyl group;

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with  $^{18}\text{F}^-$  to produce the labelled tracer of formula (II)



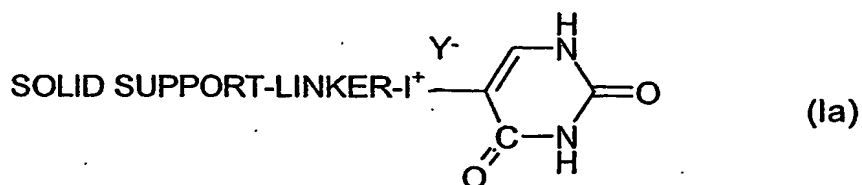
- 20 wherein  $\text{R}^1$  is as defined for the compound of formula (I);  
 optionally followed by:

- (i) removal of excess  $^{18}\text{F}^-$ , for example by ion-exchange chromatography; and/or  
 (ii) removal of any protecting groups; and/or  
 (iii) removal of organic solvent; and/or  
 25 (iv) formulation of the resultant compound of formula (II) as an aqueous solution.

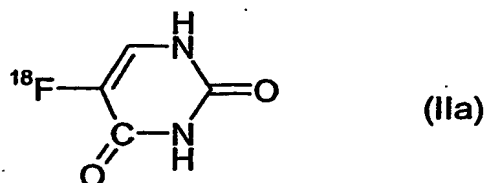
2. A process according to claim 1 for the production of  $5[^{18}\text{F}]$ fluorouracil which



comprises treatment of a solid support-bound precursor of formula (Ia):



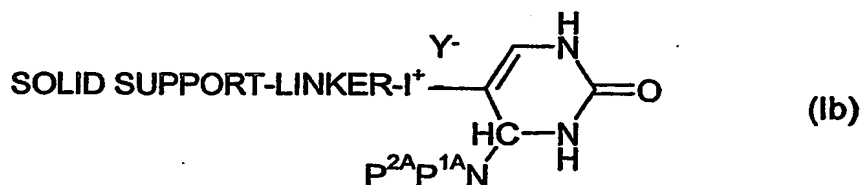
- 5 wherein Y<sup>-</sup> is an anion, preferably trifluoromethylsulphonate (triflate) anion; with <sup>18</sup>F<sup>-</sup> to produce the labelled tracer of formula (IIa)



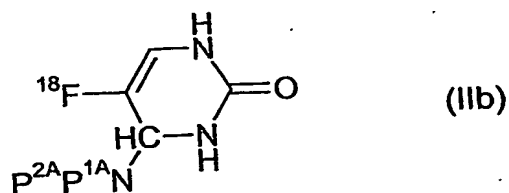
- 10 optionally followed by:

- (i) removal of excess <sup>18</sup>F<sup>-</sup>, for example by ion-exchange chromatography; and/or
- (ii) removal of organic solvent; and/or
- (iii) formulation of the resultant compound of formula (IIa) as an aqueous solution.

- 15 3. A process according to claim 1 for the production of 5[<sup>18</sup>F]fluorocytosine which comprises treatment of a solid support-bound precursor of formula (Ib):



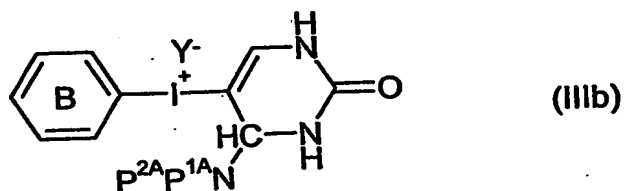
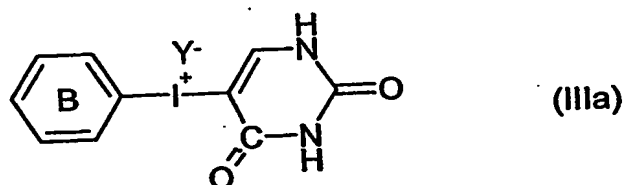
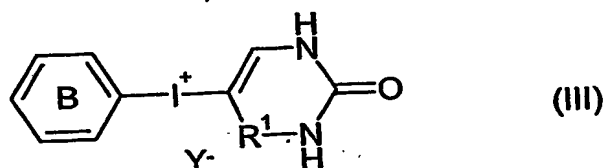
- 20 wherein Y<sup>-</sup> is an anion, preferably trifluoromethylsulphonate (triflate) anion, P<sup>1A</sup> and P<sup>2A</sup> are independently hydrogen or a protecting group; with <sup>18</sup>F<sup>-</sup> to produce the labelled tracer of formula (IIb)



wherein  $P^{1A}$  and  $P^{2A}$  are as defined for the compound of formula (Ib), optionally followed by:

- 5 (i) removal of excess  $^{18}F^-$ , for example by ion-exchange chromatography; and/or
- (ii) removal of organic solvent; and/or
- (iii) removal of any protecting groups; and/or
- (iv) formulation of the resultant compound of formula (IIb) as an aqueous solution.

- 10 4. A process for the production of an  $^{18}F$ -labelled tracer which comprises treatment of a compound of formula (III), (IIIa), or (IIIb):



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wherein  $R^1$ ,  $P^{2A}$ ,  $P^{1A}$ , and  $Y^-$  are as defined in claim 1, and phenyl ring B is optionally substituted with one to five substituents independently selected from halo,  $C_{1-6}$  alkyl,  $C_{1-6}$  haloalkyl, hydroxy,  $C_{1-6}$  alkoxy, amino,  $C_{1-6}$  hydroxyalkyl, and nitro;

- 20 with  $^{18}F^-$  to produce the labelled tracer of formula (II), (IIa), or (IIb) respectively as defined in claims 1 to 3, optionally followed by:

- (i) removal of excess  $^{18}\text{F}^-$ , for example by ion-exchange chromatography; and/or  
 (ii) removal of any protecting groups; and/or  
 (iii) removal of organic solvent; and/or  
 5 (iv) formulation of the resultant compound of formula (II), (IIa), or (IIb) as an aqueous solution.

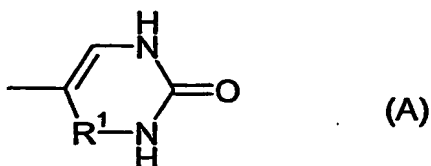
5. A process for the production of a  $^{18}\text{F}$ -labelled tracer of formula (II), (IIa), or (IIb) according to any one of claims 1 to 4, for use in PET.

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6. A compound of formula (I):

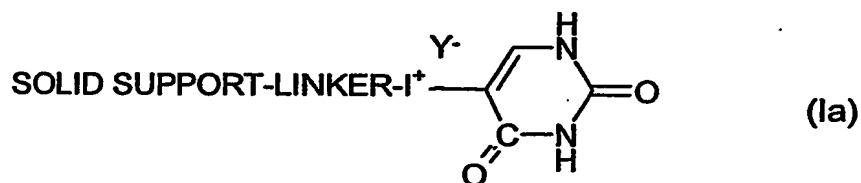


15 wherein the TRACER is of formula (A):



wherein  $\text{Y}^-$  is an anion, preferably trifluoromethylsulphonate (triflate) anion; and  
 20  $\text{R}^1$  is either (i) a group  $\text{CH-NP}^{1\text{A}}\text{P}^{2\text{A}}$  in which  $\text{P}^{1\text{A}}$  and  $\text{P}^{2\text{A}}$  are each independently hydrogen or a protecting group, or (ii) a carbonyl group.

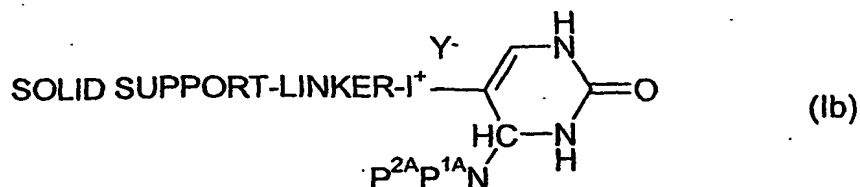
7. A compound of formula (Ia):



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wherein  $\text{Y}^-$  is an anion, preferably trifluoromethylsulphonate (triflate) anion.

8. A compound of formula (Ib):



wherein  $\text{Y}^-$  is an anion, preferably trifluoromethylsulphonate (triflate) anion,  $\text{P}^{1\text{A}}$  and  $\text{P}^{2\text{A}}$  are independently hydrogen or a protecting group.

9. A radiopharmaceutical kit for the preparation of an  $^{18}\text{F}$ -labelled tracer for use in PET, which comprises:

- (i) a vessel containing a compound of formula (I), (Ia), or (Ib) as defined in any one of claims 1 to 3 or a compound of formula (III), (IIIa), or (IIIb) as defined in claim 4; and
- (ii) means for eluting the vessel with a source of  $^{18}\text{F}^-$ ;
- (iii) an ion-exchange cartridge for removal of excess  $^{18}\text{F}^-$ ; and optionally
- (iv) a cartridge for solid-phase deprotection of the resultant product of formula (II), (IIa), or (IIb), as defined in any one of claims 1 to 3.

10. A cartridge for a radiopharmaceutical kit for the preparation of an  $^{18}\text{F}$ -labelled tracer for use in PET which comprises:

- (i) a vessel containing a compound of formula (I), (Ia), or (Ib) as defined in any one of claims 1 to 3 or a compound of formula (III), (IIIa), or (IIIb) as defined in claim 4; and
- (ii) means for eluting the vessel with a source of  $^{18}\text{F}^-$ .

11. A method for obtaining a diagnostic PET image which comprises the step of using a radiopharmaceutical kit according to claim 9 or a cartridge for a radiopharmaceutical kit according to claim 10.